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Pulmonary Function and Diffusion Capacity are Associated with Pulmonary Arterial Systolic Pressure in the General Population: The Rotterdam Study

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Abstract

Background Pulmonary hypertension is a progressive heterogeneous syndrome, characterized by elevated pulmonary arterial pressure which can lead to right ventricular failure. Although the presence of elevated pulmonary arterial systolic pressure (PASP) in patients with a lung disease is a well-known occurrence, little is known about the association between pulmonary function and PASP in the general population. We hypothesized that pulmonary function and PASP are associated, irrespective of airflow limitation.

Methods This study was performed within the Rotterdam Study, a prospective population-based cohort. We included 1,660 participants with spirometry, performed and interpreted according to ATS/ERS-guidelines, and echocardiography performed according to the ASE/EAE/CSE-guidelines. We analyzed the association of Forced Expiratory Volume in 1 second (FEV₁), Forced Vital Capacity (FVC), FEV₁/FVC and diffusion capacity (DL_{CO}) with estimated PASP (ePASP). Furthermore, we investigated the association between spirometry measures, COPD, and echocardiographic pulmonary hypertension.

Results A 10% absolute decrease in FEV₁ was associated with an ePASP increase of 0.46 mmHg (95%CI: 0.31; 0.61). Similarly, per absolute 10% decrease, FVC was significantly associated with an increased ePASP of 0.42 mmHg (95%CI: 0.25; 0.59). FEV₁/FVC showed an association of 1.01 mmHg (95%CI: 0.58; 1.45) increase in ePASP per 10% absolute decrease. A decrease in DL_{CO} (in mL/min/kPa) was associated with an increased ePASP (0.46 mmHg, 95%CI: 0.17; 0.76). We found significant associations for FEV₁ and FVC with echocardiographic pulmonary hypertension. Importantly, an increased ePASP was significantly associated with mortality (Hazard Ratio: 1.042 per mmHg [95%CI: 1.023-1.062; p<0.001]).

Conclusion We observed a clearly graded association between pulmonary function and ePASP and pulmonary hypertension, even in individuals without airflow limitation.

Introduction

Pulmonary hypertension is a progressive and in some cases fatal heterogeneous syndrome, characterized by elevated pulmonary arterial pressure and can lead to right ventricular failure [1]. Lung diseases and/or hypoxemia are important causes of pulmonary hypertension. Pulmonary hypertension is a common co-morbidity of lung disease, with a prevalence of up to 60% in patients with chronic obstructive pulmonary disease (COPD)[2]. Pulmonary hypertension in patients with COPD seems influenced by two mechanisms, obliteration of the vascular bed and hypoxia-induced vasoconstriction [3]. Its presence is associated with a progressive course of disease and decreased survival in comparison to patients with COPD without pulmonary hypertension [4]. Although the presence of elevated pulmonary arterial systolic pressure (PASP) in patients with lung disease is a well-known phenomenon, the relation between pulmonary function and PASP in the general population without lung disease is unclear.

We hypothesized that a decrease in lung function, as measured by spirometry and diffusion capacity, is associated with an increase in PASP, as measured by echocardiography, in the general population. Furthermore, we evaluated the association of ePASP with all-cause mortality.

Methods

This study was performed in the first cohort of the Rotterdam Study, an ongoing prospective population-based cohort study which started in 1990 in Ommoord, a suburb of Rotterdam. Main objectives and methods of the Rotterdam Study have been described elsewhere [5]. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the “Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)”. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. The cohort consists of 7,983 participants, aged 55 years and older. At baseline, all participants were visited at home for a standardized interview, and underwent a wide array of examinations at the research center. These study rounds are repeated every 3-5 years. Participants are actively followed for the occurrence of clinical events and mortality as detailed previously [6]. All prescriptions dispensed to the participants are collected by linkage to the seven pharmacies covering the study area.

Study population

The study population consisted of all participants of the Rotterdam Study who underwent both spirometry and echocardiography. These were gathered during the fifth study round (2009-2011).

Echocardiography

Echocardiographs were made using a commercially available ultrasonography system (Vivid I, GE Healthcare, Little Chalfont, UK), with a 2.5 MHz transducer according to a standardized protocol. Extensive left- and right-sided measurements and measures of both systolic and diastolic function were obtained. All images obtained at echocardiography were digitally stored and assessed offline by experienced echocardiographers. ePASP (in mmHg) was calculated following the recommendations by the ASE/EAE/CSE as the sum of the estimated right atrial pressure (based on the diameter of the inferior vena cava and forced respiratory collapse) and the pressure gradient over the tricuspid valve. The pressure gradient was computed from the highest Doppler tricuspid regurgitation velocity (TRV) gathered from several windows using the simplified Bernoulli equation ($4v^2$, where v is TRV in m/sec)⁸. In those with sufficient tricuspid regurgitation to estimate ePASP, a 40-mmHg cut-off was set to define echocardiographic pulmonary hypertension. The definition of echocardiography-based pulmonary hypertension (ePH) is based on the measurements of TRV (elevated TRV is defined as TRV >3 m/sec, corresponding to a ePASP of >40 mmHg) and right ventricular end-diastolic dimension (RVEDD; elevated RVEDD is defined as RVEDD >42 mm) [7–10]. If the TRV was too small to measure, but a participant had an elevated RVEDD, this was considered to be indicative of PH (Supplementary Table 1). We assessed left ventricular (LV) systolic function through LV fractional shortening in the parasternal long-axis view using M-mode. LV fractional shortening (%) at the endocardium was

calculated by: (LV end-diastolic diameter—LV end-systolic diameter) / LV end-diastolic diameter * 100% [11,12].

Spirometry and diffusion capacity

Spirometry and diffusing capacity were performed using a Master Screen® PFT Pro (CareFusion, San Diego, CA, USA) by trained paramedical personnel according to the ATS/ERS guidelines [13,14]. Using spirometry FEV₁, FVC and the ratio of FEV₁ over FVC (FEV₁/FVC) were measured. For the diffusion capacity, we measured the transfer factor using carbon monoxide in milliliters per minute per kilo Pascal (mL/min/kPA). Participants were asked to refrain from using any prescribed pulmonary medication one day before the center visit and were asked to refrain from smoking. The spirometry and diffusion capacity tests were analyzed by two researchers, and verified by a specialist in pulmonary medicine. Spirometry procedures that yielded results that did not meet ATS/ERS criteria for acceptability and reproducibility were classified as not interpretable [14]. Diffusion capacity procedures preferably attempted twice, if only one attempt was made, tests were scored on the basis of the quality of the curve. Multiple attempts yielding results that were not reproducible were not used in these analyses.

Mortality

Participants are actively followed for the occurrence of clinical events and mortality as detailed previously [6]. For the mortality analyses, the censor date was the date of last contact or date of death.

Statistical analyses

For cross-sectional analyses, we used linear and logistic regression. For mortality analyses, we used Cox proportional hazards analyses. Information on potential confounders included age, sex, height and weight, was gathered at the study in the same round as the spirometry and echocardiography. History of pulmonary embolism was determined on the basis of dispensing data of coumarin derivatives with pulmonary embolism as treatment indication through specialized monitoring centers. Furthermore, echocardiographic measures of systolic and diastolic function were collected, as well as use of medication, a history of heart failure, a history of coronary heart disease (i.e. a composite of myocardial infarction, percutaneous coronary intervention, and surgical coronary artery bypass graft), in order to adjust for left ventricular failure leading to an increased ePASP. Confounders were selected on the basis of their biologic plausibility.[6] The covariables were used in the final regression model according their influence on the effect estimate and/or statistical significance in the regression model.

Results

Within the Rotterdam Study, a total of 2,903 individuals underwent echocardiography between 2009-2011 (44% male, mean age 75 years), 1,660 individuals underwent assessment of both echocardiography and spirometry (34% male, mean age 76 years). In this dataset, a total of 284 participants had COPD according to the spirometry-based GOLD definition, of whom none had very severe airflow limitation (GOLD Stage IV). Seventy-one participants had a spirometry test suggestive of restrictive lung disease, with or without obstruction. In 1,829 participants, tricuspid regurgitation could be measured and the ePASP could be estimated in 1,660 individuals. The baseline

characteristics of these participants are shown in Table 1. In 2,380 individuals, the presence of echocardiographic pulmonary hypertension could be assessed according to the algorithm in Supplementary Table 1. Using this algorithm, 99 (4.2%) participants had echocardiographic signs of pulmonary hypertension. Data on DL_{CO} and ePASP was available in 1,294 participants. Figure 1 shows an overview of the selection of participants for the various analyses reported below.

Association of spirometry measures (FEV₁, FVC and FEV₁/FVC) and diffusion capacity (DL_{CO}) and PASP.

Using linear regression an absolute 10% decrease in FEV₁ was associated with an ePASP increase of 0.46 mmHg (95%CI: 0.31; 0.61) after adjustment for age, sex, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A-ratio, body mass index (BMI), heart rate, and use of cardiovascular drugs (beta-blockers, AT₂-receptor antagonists, high ceiling diuretics, and digoxin). Similarly, per 10% absolute decrease, FVC was associated with an increased ePASP of 0.42 mmHg (95%CI: 0.25; 0.59). Lastly, FEV₁/FVC showed an association of 1.01 mmHg (95%CI: 0.58; 1.45) increase in ePASP per absolute 10% decrease in FEV₁/FVC. (Table 2)

A decrease in DL_{CO} was associated with an increase in ePASP of 0.46 mmHg per mL/min/kPa (95% CI: 0.17; 0.76); this association remained significant after adjustment for age, sex, hemoglobin level, smoking status, pack-years, left ventricular mass, E/A-ratio, BMI, heart rate and use of cardiovascular drugs (beta-blockers, AT₂-receptor antagonists, and digoxin). (Table 2)

As a sensitivity analysis, we excluded participants with COPD and restrictive lung disease defined on the basis of spirometry (FEV₁/FVC < 0.70; n = 284, restriction n = 71). After this exclusion, the associations between the spirometric measures and ePASP persisted. For FEV₁ ePASP was associated with an increase of 0.36 mmHg (95%CI: 0.15; 0.57) adjusted for age, sex, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A-ratio, body mass index, mean heart rate, history of coronary heart disease and use of cardiovascular drugs. For FVC this increase in ePASP was 0.32 mmHg (95%CI: 0.11; 0.53). For FEV₁/FVC, a non-significant increase in ePASP was seen with an effect estimate of 0.62 mmHg (95%CI: -0.13; 1.37). In this subgroup of participants without airflow limitation, a decrease in DL_{CO} was associated with a non-significant increase in ePASP of 0.17 mmHg (95%CI: -0.17; 0.51, Table 3).

Spirometry and pulmonary hypertension

When we analyzed pulmonary hypertension dichotomously, FEV₁, FVC, and FEV₁/FVC were significantly associated with an increased risk of pulmonary hypertension, defined by echocardiography (Supplementary Table 1). Per 10% decrease, the FEV₁ was associated with an adjusted odds ratio of pulmonary hypertension of 1.18 (95%CI: 1.04; 1.34). FVC was associated with a similar adjusted odds ratio of 1.18 (95%CI: 1.02; 1.36). For FEV₁/FVC, the adjusted odds ratio was 1.30 (95%CI 0.94; 1.79). For DL_{CO}, the adjusted odds ratio was 1.05 (95%CI: 0.84; 1.31). (Table 4).

ePASP and mortality

Lastly, we analyzed the association between ePASP and all-cause mortality. In 1,652 participants with available follow-up data (mean follow-up: 3,44 years; median follow-up: 3,49 years, 180 deaths), an increased ePASP was significantly associated with mortality with a hazard ratio (HR) of 1.042 per

mmHg (95%CI 1.023; 1.062 $p < 0.001$). In participants without COPD ($n = 1,298$), ePASP was significantly associated with mortality (hazard ratio: 1.030 per mmHg, 95%CI 1.004; 1.056 $p = 0.022$). In participants with COPD ($n = 284$), ePASP was associated with mortality (hazard ratio: 1.037, 95%CI 1.004; 1.072, $p = 0.027$). These analyses were adjusted for sex, age and smoking.

Discussion

In this population-based cohort, we observed that pulmonary function was associated with PASP. In this cross-sectional analysis, there were significant associations for FEV₁ % predicted, FVC % predicted and FEV₁/FVC with ePASP as a continuous outcome and pulmonary hypertension as a dichotomous outcome, adjusted for clinically relevant confounders. For diffusion capacity, there was a significant association for PASP as a continuous variable, but a non-significant association for pulmonary hypertension, most likely due to smaller number of cases in this sample. EPASP was predictive of mortality at long-term follow-up, even after adjustment for measures of pulmonary function.

The association of the spirometric measures FEV₁, FVC, and FEV₁/FVC with ePASP is present in individuals without airflow limitation, which is indicative of COPD, or restrictive spirometry. To our knowledge this is the first time these associations are shown in the general older population, rather than in specifically designed clinic-based studies in patient populations with COPD and/or pulmonary hypertension. As demonstrated in the Rotterdam Study and many other prospective cohort studies, pulmonary function decreases over time as people age, irrespective of the presence of COPD and new reference values have been proposed [15–18]. Thus, the association found in the present study may reflect a process of worsening pulmonary function in elderly populations resulting in increasing PASP and related to the ageing process or the accumulation of deleterious exposures and damage with age. Our study might provide insight in the mechanisms of increasing PASP in a large, and otherwise relatively healthy, general population. Previously, Grossman and colleagues could not demonstrate an association between spirometry and ePASP; this was however in a population of young healthy males.[19]

Previously, Choudhary e.a. reported associations of both obstructive and restrictive spirometric measures with pulmonary hypertension in African-Americans [20]. Our results indicate that an impaired lung function, even within the normal spectrum, is associated with higher pulmonary arterial pressures. This is relevant for the life expectancy of the affected individuals. We showed a significant association between ePASP and an increased risk of all-cause mortality in this population-based study. This is in line with previous results in an aging population [21].

Limitations and strengths

A major limitation in this study is that we are not able to employ the gold standard for the diagnosis of pulmonary hypertension, which is right-heart catheterization. We were, however, quite conservative with respect to the definition of pulmonary hypertension based on echocardiography, which would more likely lead to an underestimation of the prevalence of pulmonary hypertension

[10]. Also, ePASP has been shown to correlate with invasively measured pulmonary arterial pressure, especially within the normal range of pulmonary arterial pressures, which most of the Rotterdam Study participants had [22–24]. Another limitation, due to the cross-sectional design of the study, is that it is difficult to disentangle cause and consequence and further longitudinal studies are required to clarify causality. With our sensitivity analysis, we showed effects across the full spectrum of lung function measures, independent of obstructive lung disease (the most prevalent cause of pulmonary hypertension in group 3 of the WHO Classification of pulmonary hypertension), showing that our primary associations are not driven by those participants with severely impaired lung function. Also, the prognostic implications of these slight elevations in ePASP due to reductions in pulmonary function and diffusion capacity remain to be determined. A recent study in patients with idiopathic pulmonary fibrosis showed an estimated yearly increase of PASP of 1.8 mmHg during a short follow-up [25]. This is markedly higher than the effects we report, but the participants in our study differ greatly from patients with idiopathic pulmonary fibrosis. Our data are derived from a general (aging) population, whereas the previous study included participants with a clear underlying lung disease. The mechanisms underlying increasing PASP in both groups may strongly differ. Lastly, we were able to show an increased risk of mortality with increasing ePASP, but further exploration of the mechanisms underlying these findings is needed.

The strengths of the study are the prospectively gathered population-based data, which reduces the risk of selection bias. Furthermore, we had a wide range of detailed information in this large group of older participants available (including follow-up for mortality) and, especially with respect to PH and lung function (encompassing spirometry and diffusion capacity), population-based data are scarce.

Conclusion

We show an association of pulmonary function and diffusion capacity with PASP in a general population. Furthermore, the spirometric measures FEV₁ and FVC are associated with an increased risk of pulmonary hypertension. Lastly, we showed a markedly increased risk of mortality with

increasing ePASP. The immediate clinical implications of these findings remain to be explored, but may be important in the development of new screening and diagnostic algorithms and the understanding of the biological processes leading to pulmonary hypertension.

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Study Design: A.H., H.A.G., O.F. **Data collection:** A.H., G.G.B., M.J.G.L., B.K., H.A.G., H.G., and B.H.S. **Data-analysis and writing:** D.W.L., L.L., J.F., M.J.G.L., and G.G.B. **Critical Review:** G.G.B., L.L., A.H., O.F., H.G., B.K. and B.H.S.

D.W.L and G.G.B. take responsibility for the integrity of this work.

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Characteristics		Total
Sex N (%)	Male	605 (34.4 %)
	Female	1055 (63.6 %)
Age Years (SD)		75.7 (6.3)
Height cm (SD)		165.9 (9.0)
Smoking Status [†] N (%)	Never	612 (36.9 %)
	Past	877 (52.8 %)
	Current	142 (8.6 %)
Pack Years mean (SD)		21 (21)
Blood Pressure mmHg (SD)	Systolic	151 (22)
	Diastolic	85 (11)
BMI kg/m ² (SD)		26.9 (4.0)
Echocardiography	ePASP mmHg (SD)	26.1 (6.9)
	LV mass grams (SD)	129.6 (38.1)
	LVEDD mm (SD)	51.1 (5.1)

	Fractional Shortening % (SD)	41.5 (5.7)
	E/A Ratio (SD)	0.90 (0.35)
Echographic Pulmonary Hypertension* N (%)		99 (4.2 %)
History of Coronary Heart Disease** N (%)		336 (11.6 %)
History of Heart Failure N (%)		63 (3.8 %)
Pulmonary embolism N (%)		18 (1.1 %)
Pulmonary Function	FEV ₁ L (SD)	2.29 (0.66)
	FEV ₁ percent predicted % (SD)	104 (22)
	FVC L (SD)	3.02 (0.83)
	FVC percent predicted % (SD)	109 (20)
	FEV ₁ /FVC % (SD)	76 (8)
	DL _{CO} mL/min/kPa [§]	7.13 (1.45)
GOLD Classification[¶], N (%)	No obstruction [‡]	1305 (78.6)
	I	139 (8.4 %)
	II	125 (7.5 %)
	III	20 (1.2 %)
	IV	0 (0%)

Spirometry suggestive of restriction		71 (4.3 %)
Medication use	Angiotension-2 Antagonist (%)	166 (10.0 %)
	Beta-blocking agents (%)	369 (22.2 %)
	Digoxin (%)	23 (1.4 %)
	High Ceiling diuretics (%)	76 (4.6 %)

Table 1. Baseline characteristics of the study population (n=1,660)

BMI: Body Mass Index, ePASP = estimated Pulmonary Artery Systolic Pressure, LV = left ventricular, LVEDD = Left ventricular end diastolic dimension, E/A-ratio: ratio of early and late transmitral left ventricular filling velocity, SD: Standard Deviation.† Smoking status missing: n=29.* Based on Tricuspid valve

Regurgitation Velocity and ePASP and/or secondary signs of PH such as Right Ventricle End Diastolic Dimension, total sample = 2380. ** Myocardial infarction, Coronary artery bypass graft or percutaneous coronary intervention. § n = 1,294. ¶ GOLD classification based on spirometry only.

Table 2. Effect estimates of pulmonary function measures on ePASP in mmHg

Pulmonary function test	Effect, crude	95%CI	Effect, adjusted	95%CI	P-value, adjusted
FEV₁ % predicted *	0.60	0.45; 0.75	0.46	0.31; 0.61	<0.0001
FVC % predicted *	0.62	0.46; 0.78	0.42	0.25; 0.59	<0.0001
FEV₁/FVC *	1.04	0.62; 1.47	1.01	0.58; 1.45	<0.0001
DL_{co} **	0.44	0.19; 0.69	0.46	0.17; 0.76	0.002

* per 10% decrease, n=1,660

** per decrease in mL/min/kPa, n=1,294

‡ For FEV₁, FVC and FEV₁/FVC the analyses were adjusted for: sex, age, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A ratio, BMI, heart rate, use of beta-blocking agents, use of AT₂-receptor antagonists, use of high ceiling diuretics, and use of digoxin.

For DL_{co} the analyses were adjusted for: sex, age, haemoglobin level, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A ratio, BMI, heart rate, use of beta-blocking agents, use of AT₂-receptor antagonists, and use of digoxin.

Table 3. Effect estimates of pulmonary function measures on ePASP in mmHg, excluding participants with COPD or restriction

Pulmonary function test	Effect, crude	95%CI	Effect, adjusted	95%CI	P-value, adjusted
FEV₁ % predicted *	0.49	0.29; 0.70	0.36	0.15; 0.57	0.001

FVC % predicted[*]	0.51	0.31; 0.71	0.32	0.11; 0.53	0.003
FEV₁/FVC[*]	0.73	-0.03; 1.48	0.62	-0.13; 1.37	0.106
DL_{co}^{**}	0.13	-0.14; 0.40	0.17	-0.17; 0.51	0.321

^{*} per 10% decrease, n=1,305

^{**} per decrease in mL/min/kPa, n=1,035

[‡] For FEV₁, FVC and FEV₁/FVC the analyses were

adjusted for: sex, age, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A ratio, BMI, heart rate, history of coronary heart disease, use of beta-blocking agents, use of AT₂-receptor antagonists, use of high ceiling diuretics, and use of digoxin.

For DL_{co} the analyses were adjusted for: sex, age, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A ratio, BMI, heart rate, history of coronary heart disease, use of beta-blocking agents, use of AT₂-receptor antagonists, and use of digoxin.

Table 4. Effect estimates of pulmonary function on risk of pulmonary hypertension

Pulmonary function test	OR, Crude	95%CI	OR, adjusted[‡]	95%CI	P-value, adjusted
FEV₁ % predicted[*]	1.26	1.15; 1.38	1.16	1.02; 1.31	0.021
FVC % predicted[*]	1.33	1.20; 1.48	1.17	1.01; 1.35	0.034
FEV₁/FVC[*]	1.27	1.01; 1.59	1.27	0.92; 1.77	0.149
DL_{co}^{**} mL/min/kPa	1.09	0.93; 1.28	1.05	0.84; 1.32	0.650

^{*} n=2,380

^{**} n=1,886

[‡] Adjusted for: sex, age, smoking status, pack-years, left ventricular fractional shortening, left ventricular mass, E/A ratio, BMI, heart rate, use of beta-blocking agents, use of AT₂-receptor antagonists, use of high ceiling diuretics, and use of digoxin.

Supplementary table 1. Definition of pulmonary hypertension based on echocardiography (ePH)¹

	TRV missing	TRV too small to measure, but non-missing	TRV normal, corresponding to PASP =< 40 mmHg	TRV elevated, corresponding to PASP > 40 mmHg
RVEDD missing	Missing	No ePH	No ePH	ePH
RVEDD normal	Missing	No ePH	No ePH	ePH
RVEDD elevated	ePH	ePH	ePH	ePH

RVEDD: Right ventricle end diastolic diameter, TRV: Tricuspid valve regurgitation velocity, PASP: Pulmonary artery systolic pressure.

1. Moreira EM, Gall H, Leening MJG, et al. Prevalence of pulmonary hypertension in the general population: The Rotterdam Study. *PLoS One* 2015;10(6):e0130072.

